REMARKS

The present response is submitted in reply to the Final Office Action issued on January 8, 2009. Claims 1-5, 7, 8 and 10 are pending in this application, all of which have been rejected. By the present response, claims 1 and 3 have been amended. No new matter has been added. Reconsideration is respectfully requested in light of the following remarks.

Rejection of claims 1-5, 7, 8 and 10 under 35 U.S.C. 112, second paragraph

Claims 1-5, 7, 8 and 10 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. The Examiner states that it is still not clear what is meant by the phrase "the residue of an amino acid" and asks whether the fragment includes amine, carboxylic acid, esters, alcohols or even hydrogen.

It is submitted that the aforementioned phrase has been clarified, as set forth above in the amended claims. In particular, the phrase has been amended to recited "alpha amino acid" and to define the "reside of an amino acid" by adding "the N of the ring is acylated by the carboxylic group of an amino acid" with respect to R_5 and R_7. Support can be found in the specification, such as at page 6, first paragraph.

The Applicants further submit that "the residue of an amino acid" should nevertheless be clear to one skilled in the art and that in no case can be hydrogen. One skilled in the art should readily recognize what such a residue would be, i.e., that the residue may be the residue of a naturally occurring alpha amino acid as set forth in the specification (page 6, first paragraph). The Applicants would be glad to provide a list of the naturally occurring alpha amino acids at the Examiner's request. In this regard, it is

worth pointing out that the term "residue of an amino acid" was considered definite in U.S. Patent No. 6,753,445 (e.g., claim 3), the patent having at least one inventor in common with the present application.

In view of the above, withdrawal of the rejection is requested.

Rejection of claims 1-10 under 35 U.S.C. 103(a)

Claims 1-5, 7, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,169,804 (Ascher, et al.) and/or U.S. Patent No. RE39128 (Berry, et al.). In particular, the Examiner argues that Ascher, et al. and Berry, et al. teach antibacterial mutilin compounds and compositions corresponding to those recited in the present claims, and refers to column 1, line 1 through column 2, line 34 of Ascher, et al. and column 2, lines 2-52, column 3, lines 5-10 and Examples 10, 15 and 37 of Berry, et al. The Examiner further states that while the alkyls on the corresponding R_5 substituent may differ in number, such differences in closely structured related compounds would have been obvious to one of ordinary skill in the art as the resulting products would not have been unexpected.

The Examiner also states that the previously submitted comments regarding the data was not in proper affidavit form and thus not considered.

The Applicants respectfully submit that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitation. The Applicants

respectfully submit that one skilled in the art would have no suggestion or motivation to modify and/or combine the aforementioned references in order to arrive at the presently claimed invention. Additionally, even if one skilled in the art were to consider the teachings of the cited prior art alone, or in combination, each and every limitation of the present invention would not be disclosed, nor would there be a reasonable expectation of success if the aforementioned references were to be considered either alone or in combination. In addition, prior art must be considered in its entirety, i.e., as a whole (emphasis provided), including portions that would lead away from the claimed invention (M.P.E.P. §2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220, USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)), the proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference (M.P.E.P. §2143.01), and Examiner's conclusion of obviousness may not be based on improper hindsight (M.P.E.P. §2145(X)(A)).

The Applicants respectfully traverse this rejection and respectfully submit that this rejection is in error and should not be maintained. It is first submitted that the prior art fails to teach each and every limitation of the presently amended claims as discussed above. Accordingly, the rejection should be considered improper.

The Applicants also submit herewith a declaration executed by one of the inventors – Prof. Dr. Heinz Berner – in support of the previously filed comments regarding the data. Those arguments are incorporated herein in their entirety and repeated for the Examiner's ease of reference.

The Applicants had previously enclosed *in vitro* and *in vivo* data (i.e., "screening") of (1) compounds of the present invention (i.e., WO 2004011431, which corresponds to and is the equivalent of the present application), (2) a similar compound of Ascher, et al. '804 and (3) a similar compound of Berry, et al. '128, which are elaborated upon in the attached "Materials and Methods."

In view of the previously attached data, it is respectfully submitted that the data set forth the superiority of the compounds of the present invention when compared with data obtained from compounds of Ascher, et al. '804 and Berry, et al. '128. In particular, it is submitted that the overall results of the data obtained from Examples 3 and 7 of the present application demonstrate excellent *in vitro* activity. Moreover, the aforementioned examples show excellent *in vivo* activities (e.g., ED_{50} = 8.72 mg/kg for Example 3 and 16.2 mg/kg for Example 7) as compared to the values from the cited prior art (e.g., ED_{50} = 8.83 mg/kg for Ascher, et al. '804 and 26.71 mg/kg for Berry, et al.).

It is further submitted that a comparison of the data of the most prominent example (i.e., retapamulin of Examples 50 and 58) from Berry, et al. with the data of examples of the present invention clearly set forth the improved *in vivo* activity of compounds of Examples 3 and 7 of the present invention. The improved *in vivo* efficacy is also shown by a comparison with the data of the compound of Example 1 of Ascher, et al. '804. It is submitted that these results clearly indicate improved *in vivo* activity of a compound of the present invention.

It is also submitted by the Applicants that one of the most prominent toxicities of pleuromutilins is liver toxicity. The *in vitro* hepatoxicity assay is able to indicate the hepatoxicity potential of the corresponding pleuromutilin derivative. In the *in vitro* hepatoxicity, the

compounds of Example 3 (IC_{50} = 160 μg/ml) and Example 7 (IC_{50} = 131 μg/ml) of the present invention compared to Example 1 of Ascher, et al. (IC_{50} = 63 μg/ml) show remarkable higher IC_{50} values and therefore have a definitively lower potential for *in vivo* liver toxicity.

In summary, it is submitted that the compounds of Examples 3 and 7 of the present invention have improved *in vivo* activity compared to the compounds of Examples 50 and 58 in Berry, et al. and liver toxicity is decreased compared with the compound of Example 1 of Ascher, et al. Improved efficacy of the compounds of the present invention as shown above could not be expected from either Ascher, et al. or Berry, et al., or even from a combination of the teachings of Ascher, et al. and Berry, et al., and therefore one skilled in the art would lack motivation to refer to and/or modify the teachings of the cited prior art in order to arrive at the presently claimed invention.

In view of the above, withdrawal of this rejection is strongly requested.

Conclusion

In light of the foregoing claims and arguments, it is believed that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

Date: April 8, 2009

By: _____
D. Peter Hochberg
Reg. No. 24,603

D. Peter Hochberg Co., L.P.A.
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Cleveland, OH 44114
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My name is Prof. Dr. Heinz Berner. I was born on 5.11.194 in Vienna /Austria and my current address is Geyergasse 2a, A-1180 Vienna/Austria.

I declare that,

I am a graduated chemist and professor at the Medicinal Chemistry Department of the University, Althanstrasse 14, A- 1090 Vienna (Austria) and my experience is as follows:

Synthetic Organic Chemistry as well as Synthetic Organic Electrochemistry in the fields of:
Steroids and Diterpenes
Steroid Alkaloids (Batrachotoxin)
Amino Acids
Lipopeptides and Cyclopeptolides
Heterocycles

Molecular Modelling
QSAR: Regression-, Principal Component-, Cluster- and Discriminant-Analysis

Curriculum Vitae

Born:	5.11.1940, Vienna (Austria)
High School:	Humanistisches Gymnasium, Vienna, A- 1130, Fichtnergasse 15 Matura 1958
Military Service:	1958/1959
Studies:	Chemistry, Universität of Vienna 1959-1967,
Post Doctoral Fellow:	1968-1970, ETH Zürich: Synthesis of the Steroid Alkaloid Batrachotoxin.
Habilitation:	In the field of „Pharmaceutical Chemistry"at the Formal-und Naturwissenschaftliche Fakultät der Universität Wien, 1983.
Further Studies:	Synthetic Organic Electrochemistry, University of Lund, Sweden, Department Prof. Eberson, April-June 1983.
Industry:	Since 1970 at Novartis Research Institute (Former Sandoz Research Institute, - since 1996 at Novartis/Sandoz/ABRI and successor firm NABRIVA until end of 2005.

List of Publications

Synthesis and cytotoxic activity of resveratrol-based compounds. Handler, Norbert; Saiko, Philipp; Jaeger, Walter; Szekeres, Thomas; Wacheck, Volker; Berner, Heinz; Leisser, Klaus; Erker, Thomas. Department of Medicinal Chemistry, University of Vienna, Vienna, Austria. Monatshefte fuer Chemie (2008), 139(5), 575-578. Publisher: Springer Wien, CODEN: MOCMB7 ISSN: 0026-9247. Journal written in English. AN 2008:513088 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Preparation of pleuromutilin derivatives having antibacterial activity. Ascher, Gerd; Berner, Heinz. (Biochemie Gesellschaft m.b.H., Austria). U.S. Pat. Appl. Publ. (2003), 8pp., Cont.-in-part of Appl. No. PCT/EP2001/07875. CODEN: USXXCO US 2003162831 A1 20030828 Patent written in English. Application: US 2003-339611 20030109. Priority: GB 2000-17031 20000711; WO 2001-EP7875 20010709. CAN 148:427061 AN 2008:490622 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Quantitative structure - activity relationship studies on membrane receptors inhibition by antipsychotic drugs. Application to schizophrenia treatment. Avram, Speranta; Berner, Heinz; Milac, Adina L.; Wolschann, Peter. Department of Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Rom. Monatshefte fuer Chemie (2008), 139(4), 407-426. Publisher: Springer Wien, CODEN: MOCMB7 ISSN: 0026-9247. Journal written in English. CAN 149:95648 AN 2008:366390 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Preparation of pleuromutilin derivatives for therapeutic use as antimicrobial agents. Berner, Heinz; Kerber, Gabriele. (Sandoz G.m.b.H., Austria). PCT Int. Appl. (2004), 35 pp. CODEN: PIXXD2 WO 2004011431 A1 20040205 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. Patent written in English. Application: WO 2003-EP8059 20030723. Priority: GB 2002-17149 20020724; GB 2002-17305 20020725; WO 2003-EP3215 20030327. CAN 140:146308 AN 2004:101134 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Tuberculosis treatment using pleuromutilin analogs. Ascher, Gerd; Stauffer, Friedrich; Berner, Heinz; Mang, Rosemarie. (Sandoz GmbH, Austria; Sandoz AG). PCT Int. Appl. (2003), 74 pp. CODEN: PIXXD2 WO 2003082260 A2 20031009 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SE, SG, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. Patent written in English. Application: WO 2003-EP3215 20030327. Priority: GB 2002-7495 20020328; GB 2002-17149 20020724; GB 2002-17305 20020725. CAN 139:302016 AN 2003:796465 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Preparation of antibacterial mutilins. Ascher, Gerd; Berner, Heinz; Hildebrandt, Johannes. (Biochemie Gesellschaft m.b.H., Austria). PCT Int. Appl. (2002), 30 pp. CODEN: PIXXD2 WO 2002022580 A1 20020321 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG. Patent written in English. Application: WO 2001-EP10502 20010911. Priority: GB 2000-22440 20000913; GB 2000-22439 20000913; GB 2000-24674 20001009. CAN 136:247719 AN 2002:220557 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Preparation of pleuromutilin derivatives having antibacterial activity. Ascher, Gerd; Berner,

Heinz. (Biochemie Gesellschaft m.b.H., Austria). PCT Int. Appl. (2002), 21 pp. CODEN: PIXXD2 WO 2002004414 A1 20020117 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG. Patent written in English. Application: WO 2001-EP7875 20010709. Priority: GB 2000-17031 20000711. CAN 136:102538 AN 2002:51427 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Stereospecific synthesis of (2S,4S,6S)-2-amino-4,6-dihydroxypimelic acid. Mehlfuehrer, Michaela; Thirring, Klaus; Berner, Heinz. Sandoz Forschungsinstitut, Vienna, Austria. Journal of Organic Chemistry (1997), 62(12), 4078-4081. Publisher: American Chemical Society, CODEN: JOCEAH ISSN: 0022-3263. Journal written in English. CAN 127:33837 AN 1997:335238 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Variation of amino acids within the cyclosporin-cyclophilin binding domain. Synthesis of a 21-membered cyclopeptolide. Hornich, Elisabeth; Thirring, Klaus; Berner, Heinz. Sandoz Forschungsinstitut, Vienna, Austria. Scientia Pharmaceutica (1996), 64(3/4), 463-470. Publisher: Oesterreichische Apotheker-Verlagsgesellschaft, CODEN: SCPHA4 ISSN: 0036-8709. Journal written in German. CAN 125:276566 AN 1996:577168 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Synthesis of Modified Partial Structures of the Bacterial Cell Wall. 2. Retarded Metabolism of Lipopeptides by Insertion of α -Substituted α -Amino Acids. Frauer, Alexandra; Mehlfuehrer, Michaela; Thirring, Klaus; Berner, Heinz. Sandoz Forschungsinstitut, Vienna, Austria. Journal of Organic Chemistry (1994), 59(15), 4215-22. CODEN: JOCEAH ISSN: 0022-3263. Journal written in English. CAN 122:106461 AN 1995:17560 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

A short stereoselective synthesis of cis- and trans-4-hydroxy-L-proline. Mehlfuehrer, Michaela; Berner, Heinz; Thirring, Klaus. Sandoz Forschungsinstitut, Vienna, Austria. Journal of the Chemical Society, Chemical Communications (1994), (11), 1291. CODEN: JCCCAT ISSN: 0022-4936. Journal written in English. CAN 121:158126 AN 1994:558126 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

α -Chymotrypsin catalyzed enantioselective hydrolysis of alkenyl α -amino acid esters. Schricker, Bettina; Thirring, Klaus; Berner, Heinz. Sandoz Forschungsinst., Vienna, Austria. Bioorganic & Medicinal Chemistry Letters (1992), 2(5), 387-90. CODEN: BMCLE8 ISSN: 0960-894X. Journal written in English. CAN 119:96107 AN 1993:496107 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Synthesis of modified partial structures of the bacterial cell wall. 1. Lipopeptides containing nonproteinogenic amino acids. Schneider, Helmut; Sigmund, Gerhard; Schricker, Bettina; Thirring, Klaus; Berner, Heinz. Sandoz Forschungsinst., Vienna, Austria. Journal of Organic Chemistry (1993), 58(3), 683-9. CODEN: JOCEAH ISSN: 0022-3263. Journal written in English. CAN 118:148020 AN 1993:148020 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

A combined use of quantum chemical parameters, hydrophobic and geometrical descriptors to establish QSARs of allylamine antimycotics. Hecht, Peter; Vyplel, Hermann; Nussbaumer, Peter; Berner, Heinz. Sandoz Forschungsinst., Vienna, Austria. Quantitative Structure-Activity Relationships (1992), 11(3), 339-47. CODEN: QSARDI ISSN: 0931-8771. Journal written in English. CAN 118:120808 AN 1993:120808 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Preparation of δ -glutamylglycylalanines as drugs. Berner, Heinz. (Sandoz A.-G., Switz.; Sandoz-Patent-G.m.b.H.; Sandoz-Erfindungen Verwaltungsgesellschaft m.b.H.). Eur. Pat. Appl. (1991), 27 pp. CODEN: EPXXDW EP 417803 A1 19910320 Designated States R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE. Patent written in English. Application: EP 90-117694 19900913. Priority: DE 89-3930739 19890914. CAN 116:21466 AN 1992:21466 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Electrochemical decarboxylation of L-threonine and oligopeptide derivatives with formation of N-acyl-N,O-acetals: preparation of oligopeptides with amide or phosphonate C-terminus. Seebach, Dieter; Charczuk, Roland; Gerber, Christian; Renaud, Philippe; Berner, Heinz; Schneider, Helmut. Lab. Org. Chem., ETH, Zurich, Switz. Helvetica Chimica Acta (1989), 72(3), 401-25. CODEN: HCACAV ISSN: 0018-019X. Journal written in German. CAN 112:179809 AN 1990:179809 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Protection of phenols during electrochemical oxidation. Wistrand, Lars G.; Berner, Heinz. Div. Org. Chem., Chem. Cent., Lund, Swed. Acta Pharmaceutica Suecica (1986), 23(6), 406-7. CODEN: APSXAS ISSN: 0001-6675. Journal written in English. CAN 108:150247 AN 1988:150247 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilin. Part 11. Inversion of configuration of the vinyl group at carbon 12 by reversible retro-ene cleavage. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard; Schneider, Helmut. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1986), 117(8-9), 1073-80. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 107:115807 AN 1987:515807 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilins. 10. 1,2-Transposition of the carbonyl function in the cyclopentanone moiety of the tricyclic skeleton. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard; Fischer, Gernot. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1985), 116(10), 1165-76. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 105:133050 AN 1986:533050 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Pleuromutilin derivatives and their use. Berner, Heinz; Vyplel, Hermann. (Sandoz A.-G., Switz.; Sandoz-Patent-G.m.b.H.; Sandoz-Erfindungen Verwaltungsgesellschaft m.b.H.). Eur. Pat. Appl. (1985), 16 pp. CODEN: EPXXDW EP 153277 A2 19850828 Designated States R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE. Patent written in German. Application: EP 85-810049 19850211. Priority: DE 84-3405632 19840217; DE 84-3413708 19840412. CAN 104:207054 AN 1986:207054 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Deuteration of TDM 85-530 at the sites of cytochrome P-450 dependent oxidation and its influence on the rate of degradation. Berner, Heinz; Hildebrandt, J.; Schuster, I. Sandoz Forschungsinst., Vienna, Austria. Editor(s): Spitzy, K. H.; Karrer, K. Proc. Int. Congr. Chemother., 13th (1983), 5 108/20-108/23. Publisher: Verlag H. Egermann, Vienna, Austria CODEN: 53XPA8 Conference written in English. CAN 104:161 AN 1986:161 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilin. VIII. Functionalization at C-13 by intramolecular nitrene insertion. Synthesis of 14-O-[(3-amino-1,2,4-triazol-5-yl)thioacetyl]-13-amino-19,20-dihydromutilin hydrochloride. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard; Stuchlik, Peter. Sandoz Forschungsinst., Vienna, Austria. Tetrahedron (1984), 40(5), 919-23. CODEN: TETRAB ISSN: 0040-4020. Journal written in German. CAN 101:7466 AN 1984:407466 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilins. IX. Inversion of configuration of the methyl group at carbon 6 in

the tricyclic skeleton of the diterpene pleuromutilin. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard; Stuchlik, Peter. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1983), 114(10), 1125-36. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 100:121388 AN 1984:121388 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Pleuromutilin derivatives. Berner, Heinz. (Sandoz-Patent-G.m.b.H., Fed. Rep. Ger.). Ger. Offen. (1983), 22 pp. CODEN: GWXXBX DE 3314479 A1 19831103 Patent written in German. Application: DE 83-3314479 19830421. Priority: AT 82-1651 19820428; AT 82-4270 19821124. CAN 100:120780 AN 1984:120780 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilins. V. Photoisomerization of AB-trans-anellated mutilan-11-one. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard; Schneider, Helmut. Sandoz Forschungsinst., Vienna, Austria. Tetrahedron (1983), 39(10), 1745-8. CODEN: TETRAB ISSN: 0040-4020. Journal written in German. CAN 99:158661 AN 1983:558661 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilins. VII. Base-induced transannular 1,4-hydride shift in 8-substituted pleuromutilin derivatives. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1983), 114(4), 501-7. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 99:88400 AN 1983:488400 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilin. IV. Synthesis of 14-O-acetyl-8α -hydroxymutilin. Berner, Heinz; Vyplel, Hermann; Schulz, Gerhard; Stuchlik, Peter. Forschungsinst., SANDOZ, Vienna, Austria. Tetrahedron (1983), 39(8), 1317-21. CODEN: TETRAB ISSN: 0040-4020. Journal written in German. CAN 99:71017 AN 1983:471017 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Pleuromutilin derivatives as a tool for investigating the size and the shape of the active domain of Cyt P450. Schuster, Inge; Berner, Heinz; Egger, Helmut. Sandoz Forschungsinst. Ges.m.b.H., Vienna, Austria. Developments in Biochemistry (1982), 23(Cytochrome P-450, Biochem., Biophys. Environ. Implic.), 555-8. CODEN: DEBIDR ISSN: 0165-1714. Journal written in English. CAN 98:175082 AN 1983:175082 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Chemistry of pleuromutilins. Part 3. Synthesis of 14-O-acetyl-19,20-dihydro-A-nor-mutilin. Berner, Heinz; Schulz, Gerhard; Fischer, Gernot. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1981), 112(12), 1441-50. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 97:24030 AN 1982:424030 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Pleuromutilin derivatives. Berner, Heinz; Turnowsky, Friederike; Laber, Georg; Hildebrandt, Johannes. (Sandoz A.-G., Switz.). Eur. Pat. Appl. (1980), 26 pp. CODEN: EPXXDW EP 13768 19800806 Patent written in English. Application: EP 79-105421 19791231. Priority: . CAN 94:83688 AN 1981:83688 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Ansamycins, 5. Chemistry of metacycloprodigiosins. Synthesis of 11-(5-phenyl-1H-pyrrol-2-ylmethylidene)-11H-[8](2,4)pyrrolophane-3,4-diol. Berner, Heinz; Schulz, Gerhard; Fischer, Gernot; Reinshagen, Hellmuth. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1978), 109(3), 557-66. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 90:71987 AN 1979:71987 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Ansamycins, 4: Chemistry of metacycloprodigiosins. Synthesis of 12-(3-methoxy-5-phenyl)-2-pyrrolylmethylene-2H-[9](2,4)-pyrrolophane. Berner, Heinz; Schulz, Gerhard; Reinshagen, Hellmuth. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1978), 109(1), 137-45. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 88:190518 AN 1978:190518 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Ansamycins. Part 3. Chemistry of metacycloprodigiosins. Model reactions for the synthesis

of 3-alkoxy-substituted pyrromethenes. Berner, Heinz; Schulz, Gerhard; Reinshagen, Hellmuth. Sandoz Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1977), 108(4), 915-27. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 88:105042 AN 1978:105042 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Ansamycins, 2. Chemistry of metacycloprodigiosins. Synthesis of 5-arylpyrromethenes. Berner, Heinz; Schulz, Gerhard; Reinshagen, Hellmuth. Sandoz Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1977), 108(2), 285-97. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 87:53060 AN 1977:453060 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Ansamycins, 1. Chemistry of metacycloprodigiosins, synthesis of [9](2,4)-pyrrolophane. Berner, Heinz; Schulz, Gerhard; Reinshagen, Hellmuth. Sandoz Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1977), 108(1), 233-42. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 87:22930 AN 1977:422930 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

A biological comparison of benzene with thiophene in condensed ring systems. Thieno[3,4-d]imidazoles. Berner, Heinz; Reinshagen, Hellmuth. Sandoz-Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1976), 107(1), 299-305. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 85:46501 AN 1976:446501 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Biological comparison of benzene with pyridine in condensed ring systems. Imidazo[4,5-b]pyridines and [1,2,4]triazolo[1.5-a]pyridines. Berner, Heinz; Reinshagen, Hellmuth. Sandoz Forschungsinst., Vienna, Austria. Monatshefte fuer Chemie (1975), 106(5), 1059-69. CODEN: MOCMB7 ISSN: 0026-9247. Journal written in German. CAN 84:59315 AN 1976:59315 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

1H-Imidazo[4,5-b]- or -[4,5-c]pyridine derivatives. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 3 pp. CODEN: SWXXAS CH 561209 19750430 Patent written in German. Application: CH 72-2784 19720228. Priority: . CAN 83:131597 AN 1975:531597 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

1H-Imidazo[4,5-b]pyridine derivatives. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 3 pp. CODEN: SWXXAS CH 561210 19750430 Patent written in German. Application: CH 72-2787 19720228. Priority: . CAN 83:131596 AN 1975:531596 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

1H-Imidazo[4,5-b]- or -[4,5-c]pyridine derivatives. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 3 pp. CODEN: SWXXAS CH 561208 19750430 Patent written in German. Application: CH 72-2783 19720228. Priority: . CAN 83:131595 AN 1975:531595 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

1H-Imidazo[4,5-b]- or -[4,5-c]pyridine derivatives. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 3 pp. CODEN: SWXXAS CH 560695 19750415 Patent written in French. Application: CH 72-2782 19720228. Priority: . CAN 83:79245 AN 1975:479245 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

1H-Imidazo[4,5-b]- or -[4,5-c]pyridine derivatives. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 2 pp. CODEN: SWXXAS CH 560694 19750415 Patent written in German. Application: CH 72-2781 19720228. Priority: . CAN 83:79244 AN 1975:479244 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Phenyl(2-imidazo[4,5-b]- or -[4,5-c]-pyridyl)carbinols. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 3 pp. CODEN: SWXXAS CH 560696 19750415 Patent written in German. Application: CH 72-2785 19720228. Priority: . CAN 83:79243 AN 1975:479243 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

1H-imidazo[4,5-b,]- or -[4,5-c]pyridine derivatives. Berner, Heinz; Reinshagen, Hellmuth. (Sandoz Ltd., Switz.). Patentschrift (Switz.) (1975), 2 pp. CODEN: SWXXAS CH 560697 19750415 Patent written in German. Application: CH 72-2786 19720228. Priority: . CAN 83:79242 AN 1975:479242 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Antivirals. 1. 2-(α - Hydroxybenzyl)imidazo[4,5-c]pyridine. Berner, Heinz; Reinshagen, Hellmuth; Koch, Meinrad A. Sandoz Forschungsinst., Vienna, Austria. Journal of Medicinal Chemistry (1973), 16(11), 1296-8. CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 80:424 AN 1974:424 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Constitution of tormentol (tormentoside). Pailer, Matthias; Berner, Heinz. Univ. Vienna, Vienna, Austria. Monatshefte fuer Chemie (1967), 98(5), 2082-8. CODEN: MOCHAP Journal written in German. CAN 68:22199 AN 1968:22199 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Plant substances with a nitro group. VII. Synthesis of aristolochic acid-IV methyl ester. Pailer, Matthias; Berner, Heinz; Makleit, S. Univ. Vienna, Vienna, Austria. Monatshefte fuer Chemie (1967), 98(4), 1603-12. CODEN: MOCHAP Journal written in German. CAN 67:116745 AN 1967:516745 CAPLUS (Copyright (C) 2009 ACS on SciFinder (R))

Already 1970 in Sandoz (later Novartis) I have been involved in pleuromutilin investigations, mainly, but not exclusively, in chemical synthesis of novel pleuromutilins.
In 1983 I have found the compound valnemulin which is the active ingredient in Econor®, which is a veterinary antibiotic and I am one of the inventors of the basis valnemulin patent:

Pleuromutilin derivatives and their use. Berner, Heinz; Vyplel, Hermann. (Sandoz A.-G., Switz.; Sandoz-Patent-G.m.b.H.; Sandoz-Erfindungen Verwaltungsgesellschaft m.b.H.). Eur. Pat. Appl. (1985), 16 pp. CODEN: EPXXDW EP 153277 A2 19850828 Designated States R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE. Patent written in German. Application: EP 85-810049 19850211. Priority: DE 84-3405632 19840217; DE 84-3413708 19840412.

Since 1996 in Novartis/Sandoz/ABRI and later in the successor firm NABRIVA novel pleuromutilins have been developed under my supervision.

- I am one of the inventors designated in US 2005/250811, hereinafter designated as "present invention". I have contributed to the present invention by provision of novel pleuromutilins and I have further contributed by involvement in the design and the results of activity and toxicity tests of compounds of the present invention.

I further declare that, to the best of my knowledge

- I have read and understood the inventive step argument raised by the Examiner in the Official Action issued on 05/29/2008 and in the Official Action issued on 01/29/2009.

- I also have read the response filed to the first Official Action on August 29, 2008 and I fully agree with its content.

- The EXPERIMENTS as attached to that Declaration which have been filed also in response to the first Official Action (together with the RESULTS and SUMMARY as indicated below) have been carried out at Nabriva/Novartis/Sandoz/ABRI. In these EXPERIMENTS activity and toxicity of compounds of the present invention, namely such as designated in the EXPERIMENTS, have been compared with activity and toxicity of compounds of the prior art, namely compounds such as designated in the EXPERIMENTS. The obtained results are set out in the table of the RESULTS as attached herewith.
I have considered the RESULTS obtained in these EXPERIMENTS and from the RESULTS I conclude that the compounds of the present invention have outstanding high activity and low toxicity compared with the compounds of the prior art, e.g. as set out in the SUMMARY attached herewith.

-I further conclude that, from the prior art it could not be expected that the compounds of the present invention could show such outstanding high activity and low toxicity compared with those of the prior art compounds, e.g. because of certain similarities in chemical structure of compounds of the present invention compared with the prior art compounds. Thus, I further conclude that the high activity and low toxicity of the compounds of the present invention is unobvious from the prior art and thus inventive.

Vienna/Austria 3rd of March 2009 Signature

Prof. Dr. Heinz Berner